Genetic susceptibility, plant-based dietary patterns, and risk of cardiovascular disease

Yoriko Heianza,[1] Tao Zhou,[1] Dianjianyi Sun,[1] Frank B Hu,[2,3] JoAnn E Manson,[3,4] and Lu Qi[1,2]

[1]Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA, USA; [2]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [3]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA; and [4]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

ABSTRACT

Background: Plant-based dietary patterns may be related to better cardiovascular profiles. Whether a healthy plant-based dietary index is predictive of future cardiovascular disease (CVD) across people with different genetic susceptibility remains uncertain.

Objective: We investigated associations of adherence to healthy plant-based diets with the incidence of CVD considering the genetic susceptibility.

Methods: This prospective cohort study included a total of 156,148 adults initially free of CVD and cancer. We calculated a healthful plant-based diet index (healthful-PDI) in which healthy plant foods received positive scores, and less healthy plant foods and animal foods received reverse scores. Genetic risk scores (GRSs) for myocardial infarction (MI) and stroke were calculated to assess interactions between healthful-PDI and GRSs.

Results: During 5 y of follow-up, we observed 1812 incident cases of CVD. Higher healthful-PDI was associated with a lower CVD risk [HR per 10-unit increment: 0.87 (95% CI: 0.81, 0.93) after adjusting for demographic, lifestyle, and other dietary factors (model 1); HR 0.90 (0.84, 0.97) after further adjusting for obesity and metabolic factors (model 2)]. The risk of CVD was gradually decreased in association with higher adherence to healthful-PDI, regardless of genetic susceptibility. The inverse associations of healthful-PDI with CVD were consistently observed in people with low GRS-MI [HR 0.85 (95% CI: 0.76, 0.94) in model 1; HR 0.88 (0.79, 0.97) in model 2] and those with high GRS-MI [HR 0.91 (0.82, 0.99) in model 1; HR 0.94 (0.86, 1.04) in model 2], without significant interactions ($P_{interaction} = 0.59$ in model 1; $P_{interaction} = 0.66$ in model 2). Similarly, higher healthful-PDI was related to a lower risk of CVD, regardless of low/high GRS-stroke.

Conclusion: Adherence to healthy plant-based diets may be associated with a decreased incidence of CVD in the entire population, suggesting that plant-based dietary patterns may modify the risk of CVD, regardless of genetic susceptibility. *Am J Clin Nutr* 2020;112:220–228.

Keywords: genetic risk, plant-based dietary index, plant-based nutrition, cardiovascular risk, myocardial infarction, stroke, prospective study

Introduction

Cardiovascular disease (CVD) remains a leading cause of premature death (1), and the importance of adherence to healthful dietary patterns has been widely accepted in the prevention of CVD (2, 3). Vegetarian diets typically include nutrients that have been associated with better cardiovascular risk profiles (4). A large body of evidence has suggested that vegetarian diets and plant-based diets are related to lower risks of CVD and coronary heart disease (CHD) (5–8), as well as favorable metabolic risk

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Supplemental Methods, Supplemental Tables 1–3, and Supplemental Figures 1–7 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Data, the statistical code, questionnaires, and technical processes are available from the corresponding author. Data used in this study are available through the UK Biobank (www.ukbiobank.ac.uk) upon request. Analytical methods and study materials will be available to other researchers from the corresponding authors on reasonable request for purposes of reproducing the results or replicating the procedure.

Address correspondence to LQ (e-mail: lqi1@tulane.edu).

Abbreviations used: CHD, coronary heart disease; CVD, cardiovascular disease; GRS, genetic risk score; MI, myocardial infarction; PDI, plant-based diet index; Q, quintile; SNP, single nucleotide polymorphism.

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factors for CVD (9–11). In addition to population health, plant-based foods may link to environmental sustainability and may have positive impacts on our living environment (12, 13).

In prospective studies in the USA, newly developed plant-based diet indices, which captured synergistic and graded intakes of healthy and less healthy plant-based foods as well as animal foods, were found to be associated with the incidence of CHD and type 2 diabetes (7, 11). Although such a plant-based diet index (PDI) has been proposed, the clinical utility of PDI in predicting future cardiovascular events remains uncertain in other populations with distinct characteristics from the original studies. Further, it has not been determined whether the genetic risk could impact the associations. We and others have reported that better adherence to healthier dietary patterns might modify the genetic risk of obesity, type 2 diabetes, and CHD (14–18). However, little is known about the potential interactions between adherence to plant-based dietary patterns and genetic susceptibility for the incidence of CVD.

In the present study, we aimed to investigate associations of adherence to healthful plant-based dietary patterns assessed by healthful-PDI with the incidence of CVD [myocardial infarction (MI) and stroke] among participants of the UK Biobank study. We also prospectively investigated whether associations of healthful-PDI with risks of cardiovascular events differed according to the genetic susceptibility to CVD by testing gene-diet interactions.

Methods

Study population

In the UK Biobank, participants underwent a range of measurements during the period from 2006 to 2010 and provided various information on health and diseases (19). The UK Biobank has approval from the North West Multi-Center Research Ethics Committee which covers the UK, and the Community Health Index Advisory Group, which covers Scotland. This study was covered by the general ethical approval for UK Biobank studies from National Health Service National Research Ethics Service. All participants had provided written informed consent to participate in the UK Biobank.

The present analysis included a total of 211,016 participants who completed ≥1 web-based 24-h dietary assessment during 2009–2012 and also had information on follow-up disease events based on hospital records and the death registry. We excluded individuals who had a history of MI (n = 4043) or stroke (n = 2492) before the baseline date when dietary intake was first assessed. We also excluded participants (n = 6641) with a history of cancer at recruitment (either breast cancer, gastrointestinal cancer, urinary tract cancer, or lung cancer), leaving 198,245 individuals. After further exclusions of participants with missing data on BMI, the Townsend Deprivation Index, smoking habit, dietary intake, or those with implausible total energy intake (e.g., men with <800 kcal/d or >4200 kcal/d or women with <600 kcal/d or >3500 kcal/d) (7, 11), a total of 191,445 individuals were eligible for the analyses. We recognized that 18% of the eligible study participants (n = 35,297/191,445) reported that their dietary intake for that day was not typical because of fasting, illness, or other reasons. Although this information did not appreciably alter our main results, the present study included a total of 156,148 participants who reported a typical dietary intake at the time of dietary assessment (**Supplemental Figure 1**). In analyses of gene-diet interactions, we included 152,975 individuals with available genetic data.

Dietary Assessment

Participants completed a web-based 24-h dietary assessment, the Oxford WebQ, during 2009–2012. The Oxford WebQ asks about the consumption of >200 types of foods and >30 types of drinks during the previous 24 h. A portion size was specified as amount/serving with a description of the particular serving size. The following question was also asked: "would you say that what you ate and drank yesterday was fairly typical for you (yes/no)." Daily nutrient intakes were automatically calculated. A detailed description and accuracy of the dietary assessment have been validated elsewhere (20, 21). Compared with an interviewer-administered 24-h dietary recall, the Oxford WebQ captures similar food items and estimates similar nutrient intakes with moderate to strong correlations for the majority of nutrients, with Spearman's correlation coefficients' ranges of 0.5–0.9 (21). The mean percentage differences in intake between the Oxford WebQ and interviewer-administered 24-h dietary recall were <5% for energy (0.1%) and macronutrients (1.3% for protein, 4.6% for fat, and 2% for carbohydrate) (21). It has also been reported that on rare occasions, a food item was reported in only 1 assessment method; however, this was not more frequent or systematically different between the 2 methods (21).

We assessed adherence to healthy plant-based dietary patterns using validated methods (7, 11); a total of 17 major food groups were prepared based on definitions used in the previous studies (7, 11), within larger categories of healthy plant foods, less healthy plant foods, and animal foods. As explained in previous studies (7, 11), healthy or less healthy plant-based foods were distinguished based on existing evidence on associations of the foods with cardiovascular outcomes and metabolic abnormalities. The 17 food groups (in servings per day) were ranked into quintile (Q) categories, and each quintile was assigned a score between 1 and 5. With positive scores, a score of 5 was given for the highest quintile category, following on through a score of 1 given for the lowest quintile category. With reverse scores, this pattern of scoring was inverted. Healthy plant foods (such as whole grains, whole fruits, vegetables, nuts, legumes and vegetarian protein alternatives, and tea/coffee) received positive scores, whereas less healthy plant foods (such as refined grains, potatoes, fruit juices, sugar-sweetened beverages, and sweets) and animal foods received reverse scores. Overall, healthy plant foods included food items rich in dietary fiber and plant bioactives. Consumption of potatoes was included in the less healthy plant food group to be consistent with the methods in previous publications (7, 11). It has also been reported that potato consumption was not significantly associated with decreased risks of cardiovascular events and may be related to a small increase in the risk of type 2 diabetes (22). Higher scores of healthful-PDI are related to greater adherence to healthy plant food dietary patterns (**Supplemental Table 1**). Additional information on the dietary assessment have been addressed in the **Supplemental Methods**.

TABLE 1 Characteristics of study participants according to quintile categories of healthful plant-based diet index

	Quintile 1 (n = 30,508)	Quintile 2 (n = 29,798)	Quintile 3 (n = 35,064)	Quintile 4 (n = 30,368)	Quintile 5 (n = 30,410)
Healthful plant-based diet index	47 ± 3	53 ± 1	57 ± 1	60 ± 1	66 ± 3
Age, y	54.7 ± 8.3	55.9 ± 8.1	56.3 ± 7.9	56.6 ± 7.7	56.8 ± 7.5
Male sex	17,345 [56.9]	14,776 [49.6]	15,779 [45.0]	12,223 [40.2]	10,873 [35.8]
Parental history of heart disease	11,343 [37.2]	11,729 [39.4]	14,009 [40.0]	12,459 [41.0]	12,923 [42.5]
Genetic risk score-myocardial infarction	83.8 ± 6.4	83.9 ± 6.4	83.9 ± 6.4	84.0 ± 6.5	84.0 ± 6.4
Genetic risk score-stroke	20 ± 3.7	20 ± 3.7	20 ± 3.7	20 ± 3.7	20 ± 3.7
White British ethnicity	27,141 [89]	26,631 [89.4]	31,517 [89.9]	27,229 [89.7]	27,047 [88.9]
Smoking habit					
Never	17,091 [56]	16,840 [56.5]	20,190 [57.6]	17,751 [58.5]	17,735 [58.3]
Former	10,225 [33.5]	10,387 [34.9]	12,173 [34.7]	10,678 [35.2]	11,030 [36.3]
Current	3192 [10.5]	2571 [8.6]	2701 [7.7]	1939 [6.4]	1645 [5.4]
Physical activity, MET-h/wk	38.8 ± 41.4	39.0 ± 39.5	39.6 ± 39.1	41.0 ± 39.5	43.0 ± 40.4
Townsend Deprivation Index	–1.4 ± 3.0	–1.6 ± 2.9	–1.7 ± 2.8	–1.7 ± 2.8	–1.6 ± 2.8
College or university degree	11,018 [36.1]	11,593 [38.9]	14,707 [41.9]	13,368 [44]	14,610 [48]
Income					
<£18,000	4439 [14.6]	4226 [14.2]	4762 [13.6]	4011 [13.2]	4163 [13.7]
£18,000 to £30,999	6588 [21.6]	6784 [22.8]	7715 [22.0]	6755 [22.2]	6644 [21.8]
£31,000 to £51,999	8052 [26.4]	7482 [25.1]	8974 [25.6]	7909 [26.0]	7732 [25.4]
£52,000 to £100,000	6431 [21.1]	6397 [21.5]	7741 [22.1]	6588 [21.7]	6684 [22.0]
>£100,000	1837 [6.0]	1791 [6.0]	2212 [6.3]	1917 [6.3]	1977 [6.5]
Missing	3161 [10.4]	3118 [10.5]	3660 [10.4]	3188 [10.5]	3210 [10.6]
BMI, kg/m^2	27.8 ± 4.8	27.2 ± 4.6	26.8 ± 4.5	26.5 ± 4.4	26.0 ± 4.3
Systolic blood pressure, mmHg	137 ± 18	137 ± 18	137 ± 18	137 ± 18	136 ± 19
Diastolic blood pressure, mmHg	83 ± 10	82 ± 10	82 ± 10	82 ± 10	81 ± 10
Hypertension	23,111 [75.8]	22,216 [74.6]	25,736 [73.4]	21,953 [72.3]	21,383 [70.3]
Type 2 diabetes	1194 [3.9]	1047 [3.5]	1139 [3.2]	995 [3.3]	1054 [3.5]
Dyslipidemia	4355 [14.3]	4199 [14.1]	4729 [13.5]	4024 [13.3]	3887 [12.8]
Healthful plant foods, servings/d	9.0 ± 4.0	11.3 ± 4.3	12.8 ± 4.5	14.5 ± 4.6	17.4 ± 5.2
Less healthy plant foods, servings/d	7.5 ± 3.2	5.7 ± 2.8	4.7 ± 2.5	3.8 ± 2.3	2.7 ± 1.9
Animal foods, servings/d	5.0 ± 2.4	4.0 ± 2.1	3.5 ± 1.9	3.0 ± 1.8	2.4 ± 1.6

Data are mean ± SD or N [%].
MET, metabolic equivalent task.

Calculation of genetic risk scores

To evaluate the potential influence of genetic risk on associations of healthful-PDI with cardiovascular outcomes, we analyzed gene-diet interactions and a joint effect of diet and the genetic risk of MI or stroke. We created a genetic risk score (GRS) for coronary artery disease (GRS-MI) which included 89 single nucleotide polymorphisms (SNPs) based on previous studies (23–28). A GRS for total stroke (GRS-stroke) was created based on 30 SNPs according to the previous analysis (29). Details on SNPs and calculation of the GRSs are provided in the **Supplemental Methods**. The GRSs were normally distributed; the distribution of GRSs in the present population as well as in participants with or without events are shown in **Supplemental Figures 2–3**. We confirmed that people with a high genetic risk by GRS-MI or GRS-stroke had higher risks of cardiovascular outcomes than those with a low genetic risk (**Supplemental Figures 4–6**). Associations of GRSs for the outcomes were fundamentally the same among only white British participants (detailed data not shown).

Ascertainment of CVD outcomes

The primary outcome, incident CVD, was defined as a composite endpoint of nonfatal or fatal MI or stroke (nonfatal or fatal). Incident MI or stroke were analyzed separately as secondary outcomes. The incidence of MI (30, 31) and stroke (32, 33) were based on UK Biobank's algorithms that used inpatient hospital and death registry data linked to the study. The first occurrence of MI was defined as International Classification of Diseases (ICD)10 codes: I21.X, I22.X, I23.X, I24.1, I25.2; stroke was defined as total ischemic and hemorrhagic stroke (ICD 10 codes: I60, I61, I63, I64). The selected ICD codes from hospital and death data were estimated to produce positive predictive values for any MI of 75–100%, and for any stroke of 85–90% based on systematic reviews of published studies conducted on behalf of the UK Biobank Cardiac Outcomes Group and the Stroke Outcomes Group.

Statistical analysis

The primary hypothesis was to test whether adherence to healthful plant-based dietary patterns assessed by the healthful-PDI was associated with a decreased risk of CVD. Follow-up time was calculated from the date of diet questionnaire completion until the time of the outcome event, the time of death, or the end of follow-up (2016), whichever occurred first. Participants were categorized into quintiles of healthful-PDI to estimate the risk of CVD according to levels of adherence to dietary patterns.

TABLE 2 Nutrient intake according to quintile categories of healthful plant-based diet index

	Quintile 1 ($n = 30,508$)	Quintile 2 ($n = 29,798$)	Quintile 3 ($n = 35,064$)	Quintile 4 ($n = 30,368$)	Quintile 5 ($n = 30,410$)
Healthful plant-based diet index	47 ± 3	53 ± 1	57 ± 1	60 ± 1	66 ± 3
Alcohol intake, g/d	16.1 ± 23.9	15.5 ± 22.6	14.9 ± 21.7	13.7 ± 20.4	12.1 ± 18.9
Urinary sodium, mmol/L	86 ± 44.9	76.5 ± 42.2	71.1 ± 40.4	66.8 ± 39.1	60.4 ± 37.1
Multivitamin user	7258 [23.8]	7421 [24.9]	8972 [25.6]	8058 [26.5]	8816 [29]
Food intake[1]					
Whole grains, SVs/d	1.8 ± 2.1	2.5 ± 2.3	2.9 ± 2.4	3.3 ± 2.4	3.8 ± 2.5
Fruits, SVs/d	1.5 ± 1.5	1.9 ± 1.7	2.3 ± 1.8	2.8 ± 2	3.4 ± 2.1
Vegetables, SVs/d	1.7 ± 2	2.2 ± 2.3	2.6 ± 2.4	3.1 ± 2.6	4 ± 2.9
Nuts, SVs/d	0 ± 0.3	0.1 ± 0.4	0.1 ± 0.4	0.2 ± 0.5	0.4 ± 0.7
Legumes, SVs/d	0.2 ± 0.5	0.3 ± 0.6	0.4 ± 0.6	0.5 ± 0.7	0.8 ± 0.9
Tea and coffee, SVs/d	3.8 ± 1.9	4.2 ± 1.9	4.5 ± 1.9	4.7 ± 1.8	5.1 ± 1.8
Fruit juices, SVs/d	0.6 ± 0.7	0.5 ± 0.7	0.5 ± 0.7	0.4 ± 0.6	0.3 ± 0.6
Refined grains, SVs/d	2 ± 1.7	1.3 ± 1.5	1 ± 1.3	0.7 ± 1.1	0.5 ± 0.9
Potatoes, SVs/d	0.9 ± 0.8	0.8 ± 0.8	0.7 ± 0.7	0.6 ± 0.7	0.5 ± 0.6
Sugar sweetened beverages, SVs/d	1 ± 1.2	0.6 ± 1	0.4 ± 0.9	0.3 ± 0.8	0.2 ± 0.6
Sweets and desserts, SVs/d	2.9 ± 2.2	2.4 ± 2.1	2.1 ± 1.9	1.7 ± 1.8	1.3 ± 1.5
Animal fat, SVs/d	1.3 ± 1.6	0.9 ± 1.4	0.6 ± 1.2	0.5 ± 1.1	0.3 ± 0.9
Dairy, SVs/d	1.3 ± 1.1	1.2 ± 1	1.1 ± 1	1 ± 1	1 ± 1
Egg, SVs/d	0.5 ± 0.7	0.3 ± 0.6	0.3 ± 0.6	0.2 ± 0.5	0.1 ± 0.4
Fish or seafood, SVs/d	0.4 ± 0.6	0.4 ± 0.6	0.3 ± 0.6	0.3 ± 0.6	0.3 ± 0.5
Meat, SVs/d	1.5 ± 1.3	1.3 ± 1.2	1.1 ± 1.1	1 ± 1	0.8 ± 0.9
Miscellaneous animal-based foods, SVs/d	0.1 ± 0.6	0.1 ± 0.5	0.1 ± 0.4	0 ± 0.3	0 ± 0.2
Nutrient intake					
Total energy intake, kcal/d	2295 ± 625	2123 ± 600	2032 ± 589	1955 ± 576	1910 ± 564
Total protein, %E	15.5 ± 4	16 ± 4.2	16.3 ± 4.3	16.5 ± 4.3	16.5 ± 4.2
Total fat, %E	34.7 ± 7.2	33.1 ± 7.6	32.2 ± 7.7	31.3 ± 7.9	30.5 ± 8.2
Total carbohydrate, %E	47.4 ± 8.7	48.3 ± 9.2	49 ± 9.4	49.8 ± 9.5	51.2 ± 9.7
Total sugar, g	126.9 ± 53.8	121.7 ± 52.3	118.9 ± 50.9	117.5 ± 49.3	119.5 ± 48.4
PUFAs, %E	5.9 ± 2.5	5.8 ± 2.6	5.9 ± 2.7	5.9 ± 2.7	6.3 ± 2.9
SFAs, %E	14 ± 3.7	13 ± 3.8	12.4 ± 3.8	11.7 ± 3.7	10.7 ± 3.6
Dietary fiber, g	13.7 ± 5.9	15.2 ± 6.5	16.5 ± 6.8	17.9 ± 7	20.9 ± 7.8
β-Carotene, ug	2366 ± 2442	2821 ± 2734	3180 ± 2961	3630 ± 3165	4522 ± 3709
Folate, ug	295 ± 117	300 ± 120	304 ± 121	310 ± 123	332 ± 130
Vitamin C, mg	147 ± 113	151 ± 115	155 ± 119	159 ± 120	174 ± 122
Vitamin E, mg	8.7 ± 4.3	8.7 ± 4.4	8.9 ± 4.5	9.1 ± 4.6	10.3 ± 5.1
Magnesium, mg	322 ± 97	333 ± 102	342 ± 105	353 ± 107	385 ± 118
Potassium, mg	3577 ± 1173	3652 ± 1197	3719 ± 1208	3796 ± 1203	4008 ± 1232

Data are mean ± SD or N [%].

[1] A portion size was specified as a "serving" with a description of that particular serving size in the help section of the Oxford WebQ; the majority of portion sizes were taken from "Food portion sizes" (Ministry of Agriculture, Fisheries and Food, 1993). Examples of 1 serving: 1 slice or 1 item of white/brown bread; a whole of orange; a medium-size tomato, 1 inch of cucumber; 1 sweet pepper; 1 mug/cup of tea/coffee; 1 glass (250 mL) of fruit juice; 1 can of carbonated drink, 1 bar (~50 g) of chocolate; 1 glass (250 mL) of milk; 1 whole egg; 1 medium slice pizza.

%E, percentage of total energy intake; SVs/d, servings/day.

Unadjusted overall time to CVD incidence across healthful-PDI categories was described by Kaplan–Meier analysis with log-rank testing. The proportional hazards assumption was confirmed using log-log survival plots. Cox proportional hazard regression was performed to calculate HRs for the development of CVD. Details of the assessment of covariates in the multivariate model are described in the **Supplemental Methods**. All participants had available data on all covariates except for physical activity ($n = 148,629$); the missing indicator was used if physical activity data was missing in the multivariate model. We examined the possibly nonlinear relation between the healthful-PDI and CVD risk nonparametrically with restricted cubic splines (34). We performed fully adjusted spline regression with 5 knots; the lowest value of healthful-PDI was used as a reference value with the highest 1% or lowest 1% of each score excluded in the analysis to minimize the potential impact of outliers.

The secondary aim of this study was to examine whether the associations of healthful-PDI with CVD might be different according to genetic susceptibility for cardiovascular outcomes by testing gene-diet interactions. To test gene-diet interactions for CVD events, multiplicative interaction was assessed by adding an interaction term, where GRS and healthful-PDI were treated as continuous variables. We compared HRs for CVD of healthful-PDI according to genetic risk strata (high/low GRS based on a median value). Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc.) and STATA SE 14.0 (StataCorp); the P value <0.05 was considered statistically significant.

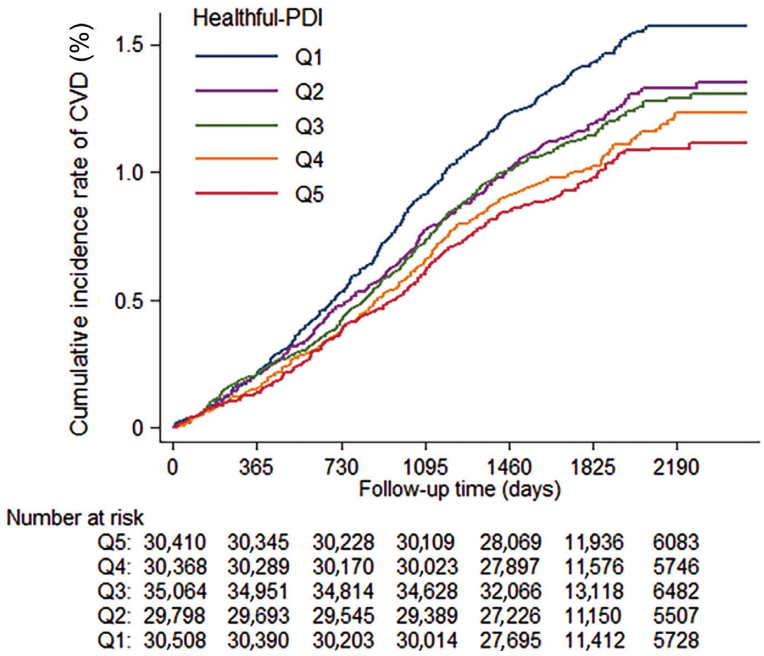

FIGURE 1 Cumulative incidence of cardiovascular disease according to quintile categories of healthful plant-based diet index. Kaplan–Meier analysis was performed to show the cumulative incidence rate across the quintiles of healthful-PDI in total participants (n = 156,148). CVD, cardiovascular disease; GRS, genetic risk score; PDI, plant-based diet index; Q, quintile.

Results

Participants in the lowest quintile (Q1) of healthful-PDI showed a mean (SD) score of 47 (3), and had 9.0 (4.0) servings/d of healthy plant foods, 7.5 (3.2) servings/d of less healthy plant foods, and 5.0 (2.4) servings/d of animal foods (**Table 1**). There was a 10-point difference in mean healthful-PDI between people with the highest adherence (Q5) and those with intermediate adherence (Q3). Individuals with higher scores of healthful-PDI were more likely to be noncurrent smokers and characterized as having lower BMI and more physically active. Higher healthful-PDI was related to greater amounts of dietary fiber, β-carotene, folate, vitamin C, vitamin E, magnesium, and potassium, as well as lower amounts of total energy intake, sugar, and SFAs (**Table 2**).

During 5 y (a total of 793,732 person-years) of follow-up, we observed 1812 incident cases of CVD. The cumulative risk of developing CVD was gradually elevated in association with lower adherence to healthful-PDI (log-rank test, P <0.0001) (**Figure 1**). In multivariate-adjusted model 1 controlling for covariates such as demographic factors, other dietary factors, and lifestyle factors [e.g., HR for current smoking compared with never smoking: HR 2.29 (95% CI: 1.98, 2.63); HR for Q5 of physical activity compared with Q1: HR 0.82 (0.71, 0.94) in the same model], healthful-PDI was inversely associated with the risk of CVD [HR for Q5: 0.77 (95% CI: 0.66, 0.90); P_{trend} = 0.0005; HR per 10-unit increment: 0.87 (0.81, 0.93)] (**Table 3**). The inverse relation between healthful-PDI and CVD risk remained significant in model 2 which controlled for additional covariates of BMI, hypertension, dyslipidemia, and type 2 diabetes (HR for Q5 category: 0.83 [95% CI: 0.71, 0.97]; P_{trend} = 0.013; HR per 10-unit: 0.90 [0.84, 0.97]). **Figure 2** shows a dose-response relation between healthful-PDI and CVD risk after controlling for the same covariates in model 2. We found a significant linear relation between healthful-PDI and CVD risk (P = 0.0056) in the spline analysis. When MI and stroke were analyzed separately (**Supplemental Table 2**), we found similar associations in model 1. The relation between healthful-PDI and MI incidence was attenuated after controlling for the covariates in model 2 [HR of Q5: 0.87 995% CI: 0.72, 1.05); HR per 10-unit increment: 0.92 (0.84, 1.00)]. Associations of healthful-PDI with stroke risk were still significant in model 2 [HR of Q5: 0.76 (95% CI: 0.60, 0.97); HR per 10-unit: 0.87 (0.78, 0.97)].

We then examined the associations of healthful-PDI and cardiovascular outcomes considering genetic susceptibility. If we tested interactions between healthful-PDI and GRS for CVD, we did not observe statistically significant interactions ($P_{gene\text{-}diet\text{-}interaction}$ between healthful-PDI and GRS-MI = 0.59; $P_{gene\text{-}diet\text{-}interaction}$ between healthful-PDI and GRS-stroke = 0.61) in model 1 controlling for demographic factors, other dietary factors, and lifestyle factors. The inverse associations of healthful-PDI with CVD risk were consistently observed in people with low GRS-MI [HR 0.85 (95% CI: 0.76, 0.94)] as well as in those with high GRS-MI [HR 0.91 (95% CI: 0.82, 0.99)] in model 1 (**Table 4**). Controlling for BMI and metabolic abnormalities in model 2 slightly attenuated the association in the high GRS-MI group [HR 0.94 (95% CI: 0.86, 1.04)]. Similarly, higher healthful-PDI was associated with a lower risk of CVD in both the low GRS-stroke group [HR 0.90 (95% CI: 0.81, 0.99)] and high GRS-stroke group [HR 0.86 (95% CI: 0.78, 0.95) in model 1]. In sensitivity analyses, the associations of healthful-PDI with MI or stroke as separate outcomes were similar, without evidence of significant GRS-healthful-PDI interactions (**Supplemental Table 3**).

Finally, we also compared HRs for CVD events (MI or stroke) according to a joint classification of healthful-PDI and

TABLE 3 HRs for cardiovascular disease according to the healthful plant-based diet index

	Quintile of healthful-PDI						Per 10-unit increment
	Q1	Q2	Q3	Q4	Q5	P_{trend}	
Median (ranges) of healthful-PDI	47 (29–50)	53 (51–54)	57 (55–58)	60 (59–62)	65 (63–85)	—	57 (29–85)
Number of participants	30,508	29,798	35,064	30,368	30,410	—	156,148
Incident cases/PYs	432/154,594	355/151,119	406/177,972	320/154,585	299/155,462	—	1812/793,732
Incident rate per 1000 PYs	2.79	2.35	2.28	2.07	1.92	—	2.28
Age-sex-ethnicity-adjusted model, HR (95% CI)	1.00 (Reference)	0.82 (0.71, 0.94)	0.81 (0.71, 0.93)	0.75 (0.65, 0.87)	0.72 (0.62, 0.84)	<0.0001	0.84 (0.79, 0.90)
Multivariate-adjusted model 1, HR (95% CI)	1.00 (Reference)	0.84 (0.73, 0.97)	0.84 (0.74, 0.97)	0.80 (0.69, 0.92)	0.77 (0.66, 0.90)	0.0005	0.87 (0.81, 0.93)
Multivariate-adjusted model 2, HR (95% CI)	1.00 (Reference)	0.87 (0.75, 0.999)	0.88 (0.77, 1.01)	0.84 (0.72, 0.97)	0.83 (0.71, 0.97)	0.013	0.90 (0.84, 0.97)

Cox regression models were performed to calculate HRs and 95% CIs. Multivariate-adjusted model 1 included covariates of age (continuous), sex, ethnicity, education, parental history of heart disease, smoking habit (never, former, current), physical activity (quintiles), multivitamin use, total energy intake (quintiles), alcohol consumption (none, >0 to 5 g/d, 5 to <15 g/d, and 15 g/d or more), and Townsend Deprivation Index (quintiles).

Multivariate-adjusted model 2 included covariates in model 1 + BMI (continuous), hypertension, dyslipidemia, and type 2 diabetes.

PDI, plant-based diet index; PYs, person-years; Q, quintile.

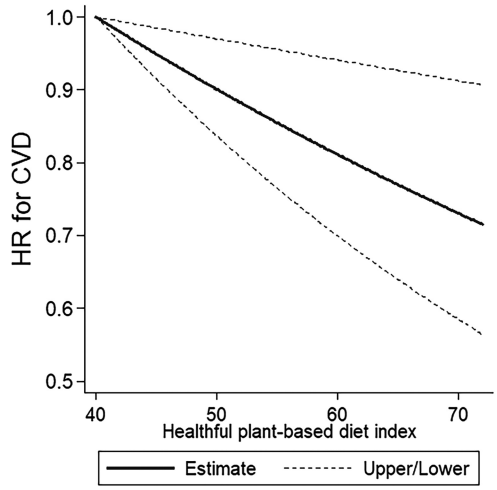

FIGURE 2 Risk of cardiovascular disease by healthful-plant-based diet index. Spline regression was performed with 5 knots, and the lowest value of healthful-PDI (a score of 40) was used as a reference value with the highest 1% or lowest 1% of healthful-PDI scores excluded in the analysis to minimize the potential impact of outliers (total n = 153,428 including 1770 events; score ranges in the spline analysis: 40–72). HR (95% CI) after controlling for age, sex, ethnicity, education, parental history of heart disease, smoking habit, physical activity, multivitamin use, total energy intake, alcohol consumption, Townsend Deprivation Index, BMI, hypertension, dyslipidemia, and type 2 diabetes. CVD, cardiovascular disease; PDI, plant-based diet index.

genetic risk status (high/low GRS based on the median value) to further investigate the extent to which genetic risk might modify the association of healthful-PDI with CVD risk (**Table 5**). Overall, the risk of CVD was gradually decreased in association with higher adherence to healthful-PDI, regardless of genetic susceptibility (Table 5 and **Supplemental Figure 7**). Compared with a reference group at the highest risk (i.e., people at a high genetic risk and with the lowest dietary adherence), people at a low genetic risk by GRS-MI and with the highest dietary adherence (healthful-PDI: Q5) showed an adjusted HR of 0.70 (95% CI: 0.57, 0.87) for CVD in model 2. Similarly, people at a low genetic risk by GRS-stroke and with the highest dietary adherence showed an adjusted HR of 0.74 (95% CI: 0.60, 0.91) for CVD compared with a reference.

Discussion

We showed that plant-based dietary patterns assessed by healthful-PDI were predictive of CVD events in the UK population. We did not find statistically significant interactions between GRS and healthful-PDI for CVD risk, suggesting that high adherence to plant-based dietary patterns was associated with a lower risk of CVD in the entire population. In addition, people with elevated scores of GRS were at a genetically higher risk of disease incidence, and higher adherence to healthful plant-based diets was associated with a lower risk of CVD regardless of genetic susceptibility.

Vegetarian diets typically have lower intakes of total fat, SFAs, and alcohol, and higher intakes of fiber and potassium (4), and a similar trend was present in this study. Further, differences in characteristics across healthful-PDI scores were consistent with previous studies (7, 11), indicating that we could reasonably categorize the participants using healthful-PDI. In line with

TABLE 4 Risk of cardiovascular disease per 10-unit increment in healthful-plant-based diet index after stratifying participants by low or high genetic risk score

Genetic risk strata	Incident cases/ person-years	Age-sex-ethnicity-adjusted model		Multivariate-adjusted model 1		Multivariate-adjusted model 2	
		HR (95% CI)	$P_{gene\text{-}diet\text{-}interaction}$	HR (95% CI)	$P_{gene\text{-}diet\text{-}interaction}$	HR (95% CI)	$P_{gene\text{-}diet\text{-}interaction}$
Low GRS-MI	796/389,042	0.82 (0.74, 0.91)	0.59	0.85 (0.76, 0.94)	0.59	0.88 (0.79, 0.97)	0.66
High GRS-MI	993/388,420	0.86 (0.79, 0.95)		0.91 (0.82, 0.99)		0.94 (0.86, 1.04)	
Low GRS-stroke	835/388,767	0.87 (0.79, 0.96)	0.63	0.90 (0.81, 0.99)	0.61	0.93 (0.84, 1.03)	0.63
High GRS-stroke	954/388,695	0.82 (0.75, 0.90)		0.86 (0.78, 0.95)		0.90 (0.81, 0.99)	

Low/high GRS was indicated by a median value. Cox regression models were performed to calculate HRs and 95% CIs.

Age-sex-ethnicity-adjusted model included age, sex, ethnicity, and the top 5 ancestry principal components.

Multivariate-adjusted model 1 included age, sex, ethnicity, education, Townsend Deprivation Index, smoking habit, multivitamin use, total energy intake, alcohol consumption, and physical activity.

Multivariate-adjusted model 2 included covariates in model 1 + BMI, hypertension, dyslipidemia, and type 2 diabetes.

$P_{gene\text{-}diet\text{-}interaction}$ values: interactions between each GRS and healthful-PDI for CVD.

CVD, cardiovascular disease; GRS, genetic risk score; MI, myocardial infarction; PDI, plant-based diet index.

results in US cohorts (7), we showed that even a slightly lower intake of animal foods and less healthy plant foods combined with a higher intake of healthy plant foods were associated with a decreased risk of CVD, independent of lifestyle factors, obesity, and metabolic factors. Moreover, we observed that the magnitude of adherence to healthful-PDI (HR 0.77 in Q5 of healthful-PDI) was similar or even larger compared with that of being physically active (HR 0.82 in Q5 of physical activity). In the Nurses' Health Study and Health Professionals Follow-up Study, per 10-unit increment in healthful-PDI, there was a 16% decreased risk (HR 0.84) in an age-adjusted model and a 12% decreased risk (HR 0.88) in a multivariate-adjusted model for CHD incidence (7), showing that the magnitude was similar to our results. According to results of the PREDIMED trial (Prevención con Dieta Mediterránea), adherence to a dietary pattern that emphasized plant-derived foods was significantly associated with a decreased risk of CVD mortality (35). Associations of vegetarian diets with lower cardiovascular mortality have been observed in the Adventist Health Study (36). Our results were also in line with a meta-analysis showing that a vegetarian diet was related to a 25% decreased risk of ischemic heart disease (6) although some studies in US populations have shown no associations of plant-based dietary patterns with CHD incidence or CVD mortality (37, 38). As for biological mechanisms for the observed results, several pathways might be involved, such as low energy density, cholesterol-lowering effects of plant bioactives like phytosterols (39), antioxidant activity of phytochemicals (40), different food sources of protein (41), and different metabolomic profiles

TABLE 5 HRs for cardiovascular disease according to a joint classification of genetic risk status and adherence to healthful-plant-based diet index

Genetic risk strata Levels of adherence to dietary patterns	Incident cases/PYs	Incidence rate per 1000 PYs	Age-sex-ethnicity-adjusted HR	Multivariate-adjusted HR, model 1	Multivariate-adjusted HR, model 2
High GRS-MI					
Low adherence (healthful PDI quintile, Q: Q1)	236/75,043	3.14	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Intermediate adherence (Q2–Q4)	595/236,803	2.51	0.81 (0.70, 0.94)	0.85 (0.73, 0.99)	0.89 (0.76, 1.04)
High adherence (Q5)	162/76,574	2.12	0.71 (0.58, 0.87)	0.77 (0.63, 0.95)	0.83 (0.68, 1.02)
Low GRS-MI					
Low adherence (Q1)	191/76,489	2.50	0.81 (0.67, 0.98)	0.81 (0.67, 0.98)	0.82 (0.68, 0.99)
Intermediate adherence (Q2–Q4)	471/236,935	1.99	0.63 (0.54, 0.74)	0.66 (0.56, 0.77)	0.70 (0.59, 0.82)
High adherence (Q5)	134/75,618	1.77	0.60 (0.48, 0.74)	0.65 (0.52, 0.80)	0.70 (0.57, 0.87)
High GRS-stroke					
Low adherence (Q1)	237/75,939	3.12	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Intermediate adherence (Q2–Q4)	565/236,358	2.39	0.76 (0.65, 0.89)	0.80 (0.69, 0.93)	0.83 (0.71, 0.97)
High adherence (Q5)	152/76,398	1.99	0.67 (0.54, 0.82)	0.72 (0.59, 0.89)	0.77 (0.63, 0.95)
Low GRS-stroke					
Low adherence (Q1)	190/75,594	2.51	0.80 (0.66, 0.96)	0.79 (0.66, 0.96)	0.79 (0.66, 0.96)
Intermediate adherence (Q2–Q4)	501/237,380	2.11	0.67 (0.57, 0.78)	0.70 (0.60, 0.82)	0.73 (0.62, 0.85)
High adherence (Q5)	144/75,793	1.90	0.63 (0.51, 0.78)	0.69 (0.56, 0.85)	0.74 (0.60, 0.91)

Cox regression models were performed to calculate HRs and 95% CIs.

Age-sex-ethnicity-adjusted model included age, sex, ethnicity, and the top 5 ancestry principal components.

Multivariate-adjusted model 1 included age, sex, ethnicity, education, Townsend Deprivation Index, smoking habit, multivitamin use, total energy intake, alcohol consumption, and physical activity.

Multivariate-adjusted model 2 included covariates in model 1 + BMI, hypertension, dyslipidemia, and type 2 diabetes.

Adherence to dietary patterns: high adherence was indicated by the highest quintile (Q5) of healthful-PDI; intermediate adherence was indicated by Q2–Q4 of healthful-PDI; low adherence was indicated by Q1 of healthful-PDI.

GRS, genetic risk score; MI, myocardial infarction; PDI, plant-based diet index; PYs, person-years; Q, quintile.

between vegetarians and animal food consumers (42–44). Plant foods with low glycemic index may also play roles in reducing platelet aggregation (45).

It has been noted that risks of MI and CVD conferred by chromosome 9p21 SNPs were modified by the intake of vegetables and fruits (15, 16). In contrast, higher consumption of sugar-sweetened beverages strengthened the effects of this gene variant on coronary artery disease (17). Other previous studies examining risk factors of CVD, such as obesity, found significant gene-diet interaction associations (18, 46); the effect of improving diet quality was more prominent in people at high genetic risk of obesity than in those with low genetic risk (18). In the present study, we introduced polygenic risk scores for MI and stroke, and we did not find significant differences in the associations of healthful-PDI with CVD incidence according to genetic susceptibility. We found that adherence to healthful-PDI was associated with a lower incidence of CVD even among people at genetically low risk, suggesting that adherence to healthy plant-based dietary patterns would be a key dietary recommendation, including people with low genetic risk. On the other hand, people with high GRS scores had an elevated absolute risk of CVD. The applications of GRSs, not only just to identify high-risk groups, but also to assess responses to interventions across the distribution of scores, have been widely discussed (47, 48). Our results and those of other studies suggest that dietary interventions focusing on plant-based dietary patterns may be considered as a targeted approach for CVD prevention across people with different GRS scores.

In this study, we introduced a previously defined dietary index to capture plant-based dietary patterns, rather than creating a new dietary pattern in this population by a data-driven approach (such as principal component analysis and factor analysis). Both predefined and data-driven approaches are useful to quantify adherence to dietary patterns (49). Whether novel dietary patterns in the UK Biobank derived using exploratory methods are related to the incidence of major chronic diseases merit further investigation. Nonetheless, evidence-based dietary guidelines (2, 3) recommend a food-based approach that prioritizes a higher consumption of healthful plant-based foods and a lower consumption of less healthy plant-based foods and animal foods for the prevention of chronic diseases.

Our study has several strengths. The present analysis shows the validity of dietary assessment in a large number of participants regarding the ability to predict the risk of CVD. The accuracy of the dietary assessment tool has been validated, and we also considered vegetarian alternative foods to create the healthful-PDI. Nonetheless, several limitations should be considered. First, similar to other studies, a challenging aspect for large cohorts is to accurately quantify diets of participants, and we cannot exclude the possibility of misclassification by participants. The dietary assessment was based on 24-h recall in UK Biobank which may be subject to short-term recall error, as well as limitations in representing habitual, long-term dietary habits. Second, we could not quantify amounts of oils and thus could not capture the effects of different types of oil intake. Thirdy, we could not assess stroke subtypes due to the limited number of incident cases. Fourth, the present study only included participants who completed the web-based dietary assessment in UK Biobank, and these people may not be representative of the general population in the UK. Further research is necessary to confirm our findings, especially in populations that are more representative of the UK population. Lastl, although we carefully considered traditional risk factors in multivariate analyses, there might be effects of residual or unmeasured confounding factors in observational studies.

In conclusion, adherence to plant-based diets assessed by healthful-PDI was associated with a decreased incidence of CVD in the entire population, and higher adherence to healthful plant-based diets may be related to a lower risk of CVD regardless of genetic susceptibility of CVD assessed by GRS-MI or GRS-stroke.

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